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Negative Correlation between Serum Brain-derived Neurotrophic Factor Levels and Obesity Predictor Markers and Inflammation Levels in Females with Obesity

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Abstract

BACKGROUND: Obesity has been widely associated with structural and functional changes in brain, whereas inflammation is one of the potential mechanisms involved in these changes.

AIM: This study aims to prove the relationship between serum brain-derived neurotrophic factor (BDNF) levels and obesity predictor markers (body mass index [BMI] and waist to hip ratio [WHR]) and inflammation (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]) levels of in females with obesity.

METHODS: This study used a cross-sectional study method using 33 female with obesity aged 19–23 years, BMI >27.5 kg/m^2, normal blood pressure, normal resting heart rate, normal hemoglobin, and fasting blood glucose ≤100 mg/dL. The examination of serum BDNF, IL-6, and TNF-α levels using the Enzyme-Linked Immunosorbent Assay method. The data were analyzed using Pearson product-moment test with a significant levels $p < 0.05$.

RESULTS: The results indicated that there is a negative correlation between serum BDNF levels and BMI ($r = –0.759$; $p < 0.001$), WHR ($r = –0.675$; $p < 0.001$), IL-6 levels ($r = –0.530$; $p < 0.001$), and TNF-α levels ($r = –0.561$; $p < 0.001$).

CONCLUSION: Based on the results of the study, there is a negative correlation between serum BDNF levels and BMI, WHR, and inflammation (IL-6 and TNF-α) levels in females with obesity. Further studies are needed to confirm the present findings.

Introduction

The worldwide prevalence of obesity nearly tripled between 1975 and 2016 [1]. Based on data from the WHO [1] reports, around 13% of the world's population aged 18 years in 2016 were categorized as obese. Obesity is regarded as a condition of excessive fat accumulation, and thus it can affect individual health [2]. According to Wang *et al*. [3], individuals with obesity have a lower life expectancy and have a higher risk of premature death than those with normal weight [4]. Today's obesity is also a major contributor to public health problems since it increases the risk factors for chronic non-communicable diseases, such as cardiovascular disease, non-alcoholic fatty liver disease, diabetes mellitus type II, and several types of cancer [5], [6].

A study conducted by Nota *et al*. [7] reported that obesity has also been associated with structural and functional changes in the brain. Potential mechanisms in these changes include inflammation and vascular and metabolic changes [8]. Recently, obesity has also been associated with a low-grade inflammatory state [9], [10], [11]. This condition triggers systemic inflammation which becomes an important factor for microglial activation and neuroinflammation in neurodegeneration [12]. This is caused by excess macronutrients in adipose tissue stimulating the release of inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and decreasing the production of anti-inflammatory agents, such as adiponectin [13]. The results of a study conducted by Calabrese *et al*. [13] indicated that the production of pro-inflammatory cytokines significantly reduces the expression of brain derived neurotrophic factor (BDNF). The decrease in BDNF expression has been widely associated with cognitive dysfunction and dementia [14], [15], [16], [17], [18], [19], [20], [21], [22].

BDNF dysregulation is not only associated with the pathogenesis of neurodegenerative and psychiatric disorders, but also inflammation, metabolism, and cardiovascular disease [23].

BDNF is the most expressed neurotrophin in the brain and plays a key role in learning and memory, especially in cognitive function [23]. A current study have revealed that activation of tropomyosin receptor kinase B (TrkB) by BDNF can stimulate the signaling pathways of mitogen-activated protein kinase/ERK, phosphatidylinositol 3-kinase/Akt, and phospholipase C-gamma [24]. Intensive investigations into this signaling had been performed since BDNF/TrkB-mediated intracellular signaling is involved in many neuronal aspects [25]. The BDNF regulates brain function and acts as a neuroprotective through the mechanism of increasing neurogenesis, neuronal survival, axonal growth, dendritic growth, synaptic plasticity, neuronal development, and maintenance in the central nervous system neurons [24]. The BDNF is also associated with the pathophysiology of obesity and metabolic syndrome [26]. However, the relationship of BDNF and obesity is still not clearly revealed. The results of the meta-analysis conducted by Sandrini *et al*. [27] showed that obesity is not associated with a decrease in circulating BDNF levels. However, the study conducted by of Goltz *et al*. [28] reported that BDNF levels is correlated with central obesity. In addition, the relationship between BDNF levels and inflammation levels is still controversial. A study conducted by Patas *et al*. [29] reported that BDNF levels is correlated with IL-6 levels and has no correlation with TNF-α levels. However, the results of a study conducted by Zhang *et al*. [30] showed that the BDNF levels are not correlated with IL-6 and TNF-α levels. On this basis, the objective of this study is to analyze the relationship between serum BDNF levels and predictor markers of obesity (body mass index (BMI) and waist to hip ratio [WHR]) and inflammation levels (IL-6 and TNF-α) in adolescent girls with obesity. The authors hypothesized that there is a significant correlation between serum BDNF levels and predictor markers of obesity and inflammation levels in adolescent girls with obesity.

Methods

Research design

The authors used a cross-sectional study method by employing 33 female with obesity aged 19–23 years with BMI >27.5 kg/m^2, normal blood pressure, normal resting heart rate (RHR), hemoglobin (Hb) normal, and fasting blood glucose (FBG) ≤100 mg/dL. All respondents received information orally and in writing about the research. They were required to fill out and sign an informed consent before participating in the study.

Ethical clearance

All research procedures have been approved by the Health Research Ethics Commission, Faculty of Medicine, Universitas Brawijaya Malang number 81/EC/KEPK–S1/04/2020.

Analysis of obesity predictor markers

The height of the respondents was measured using a stadiometer (SECA, Chino, CA, USA), while the body weight was measured using an electronic scale (Tech 05®, China). The BMI was measured by calculating body weight (kg) divided by height in m^2 [31]. The blood pressure was measured using an OMRON digital blood pressure meter (OMRON Model HEM-7130 L, Omron Co., Osaka, Japan). The waist circumference (WC) was measured by circling the anthropometric tape measure on the halfway between the lower rib and iliac bones parallel to the midaxillary straight line. The hip circumference (HC) was measured by circling the anthropometric tape measure right on the great trochanters, while the waist to WHR measurement was performed by calculating its WC divided by HC.

Analysis of BDNF and inflammatory levels

The blood was taken from the cubital vein amounted to 4 ml after undergoing overnight fasting for 12 h. The respondents were asked to do sleeping position while the blood was taken. The collected blood was centrifuged for 15 min at 3000 rpm. The serum was separated and stored at −30°C for obtaining an analysis of BDNF, IL-6, and TNF-α levels in the next day. The blood sampling was performed at 07.00–08.00 a.m. (Jakarta time). The measurement of serum BDNF levels was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) kit method (Catalog No. E-EL-H0010; Elabscience, Inc., China) with a standard curve range of 31.25–2000 pg/mL and the sensitivity levels of BDNF in the kit 18.75 pg/mL. The IL-6 levels were measured using ELISA kit method (Catalog No. E-EL-H0102; Elabscience., China) with a standard curve range of 7.81–500 pg/mL and the sensitivity levels of IL-6 in the kit was 4.69 pg/mL. The TNF-α levels were measured using the ELISA kit method (Catalog No. E-EL-H0109; Elabscience, Inc., China) with a standard curve range of 7.81–500 pg/mL and sensitivity 4.69 pg/mL. Blood taking for examination of FBG and Hb levels was carried out in the capillaries located at the tip of the middle finger. The FBG examination was performed using Accu-Chek Performance (Roche, Mannheim, Germany) with the levels of mg/dL, while the Hb examination was performed using Easy Touch GCHb (Easy Touch, Hsinchu, Taiwan) with the levels of g/dL.

Statistical analysis

The statistical analysis technique was performed using Statistical Package for the Social Science (SPSS) software version 21 (SPSS Inc., Chicago, IL, USA). The normality test was made using Kolmogorov–Smirnov test. Data with normal distribution were tested using Pearson product-moment with significant levels of $p < 0.05$. All data were then displayed with the mean ± standard error of the mean.

Results

The analysis on the characteristics of respondents showed several results, that is, the mean age (20.76 ± 0.19 years), anthropometric parameters of height (1.57 ± 0.01 m), body weight (73.02 ± 1.48 kg), BMI (29.55 ± 0.52 kg/m^2), WC (87.61 ± 2.03 cm), HC (107.58 ± 1.27 cm), WHR (0.80 ± 0.01), SBP (113.82 ± 0.68 mmHg), DBP (76.06 ± 0.85 mmHg), RHR (73.18 ± 1.08 bpm), FBG (88.00 ± 1.04 mg/dL), and Hb (14.65 ± 0.14 g/dL). The mean serum BDNF levels showed (341.33 ± 18.97 pg/mL) and the mean inflammation levels showed IL-6 (10.03 ± 0.79 pg/mL) and TNF-α (17.91 ± 0.40 pg/mL). The relationship between serum BDNF levels and BMI, WHR, IL-6, TNF-α is presented in Figure 1.

Based on Figure 1, the results of the Pearson product-moment linear correlation parametric analysis indicates that there is a negative correlation between serum BDNF levels and BMI ($r = –0.759$; $p < 0.001$), WHR ($r = –0.675$; $p < 0.001$), IL-6 levels ($r = –0.530$; $p < 0.001$), and TNF-α levels ($r = –0.561$; $p < 0.001$).

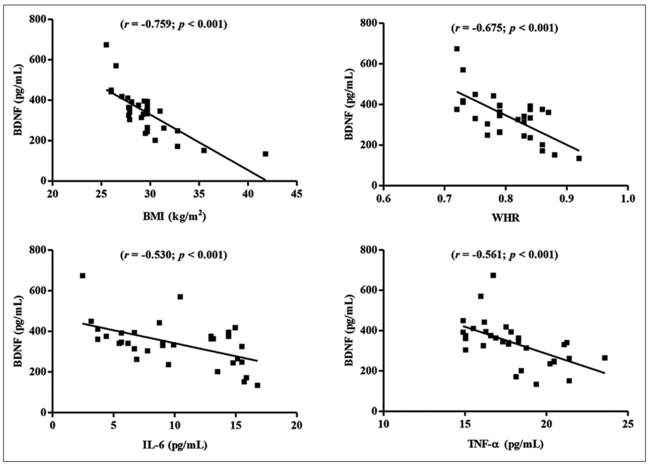

*Figure 1: Negative correlation between serum brain-derived neurotrophic factor levels and body mass index, waist to hip ratio, interleukin-6, and tumor necrosis factor-α. *Significant with $p < 0.05$ by Pearson's product-moment correlation test*

Discussion

The results of the analysis showed that there was a negative correlation between serum BDNF levels and BMI and WHR (Figure 1). These results are in line with the results of a study conducted by Si *et al*. [32] that there is a negative correlation between BMI and BDNF levels in male and female students. A study conducted by Yang *et al*. [33] also reported that BDNF levels have a significant correlation with BMI in female. Furthermore, a study conducted by Jung *et al*. [34] confirmed that BDNF levels have a correlation with BMI. Zhang *et al*. [35], through his study, also reported that BDNF levels are associated with BMI. Goltz *et al*. [28] in his research also reported that BDNF levels correlated with WHR in obese individuals. These finding confirm that there is a relationship between BDNF levels and predictor markers of obesity. This relationship may be underlined by a significant reduction in BDNF levels in individuals with obesity [36]. The study conducted by El-Alameey *et al*. [26] proved that children with obesity have a significant decrease in serum BDNF levels. Besides, the study conducted by El-Gharbawy *et al*. [37] also reported that serum BDNF is lower in children and adolescents with obesity than children and adolescents with normal or ideal weight. The decrease in BDNF levels can inhibit the activation of tropomyosin kinase B (TrkB) receptors and primary BDNF receptors, resulting in hyperphagia and obesity [38]. The inhibition in activation between BDNF and TrkB triggers a series of reactions that inhibit an eager to eat and weight gain [38]. This shows that BDNF has a central role in inhibiting appetite, thereby increasing negative energy balance dsa[36]. Being overweight and obese in early adulthood are associated with a higher risk of cardiovascular disease in future life, and it also has a negative impact on academic performance and executive control which is characterized by accelerated cognitive decline and brain atrophy in later years [32].

Based on the results of statistical analysis, there is a negative correlation between serum BDNF levels and inflammation levels (IL-6 and TNF-α) in female with obesity (Figure 1). These results are in line with the results of study conducted by Patas *et al*. [29] that BDNF levels have a correlation with IL-6 levels, but the BDNF levels do not have a relationship with TNF-α levels in patients with major depressive disorder (MDD). These results are also different from that of the study conducted by Zhang *et al*. [30] that BDNF levels do not have correlation with IL-6 and TNF-α levels in patients with chronic schizophrenia. The difference may be caused by the fact that this study used female with obesity as the respondents, whereas the previous studies used chronic schizophrenia patients and MDD patients. It has recently been reported that obesity is associated with a low-grade inflammatory state [9], [10], [27]. Such a condition triggers systemic inflammation which is an important factor for microglial activation and neuroinflammation in neurodegeneration [11]. This may happen due to excess macronutrients in adipose tissue that stimulate the release of pro-inflammatory mediators, such as TNF-α and IL-6 and reduce the production of anti-inflammatory agents, such as adiponectin [12]. The results of a study conducted by Calabrese *et al*. [13] revealed that an increase in production of pro-inflammatory cytokines significantly reduces the BDNF levels.

Based on the results of a review conducted by Sui and Pasco [39], obesity also has a relationship with a decrease in cognitive finction, neuronal plasticity, brain volume, and brain structure. Besides, the changes in BDNF levels are affected by genetic factors, but other evidence also showed that BDNF levels are associated with the changes in lifestyle and dietary habit [39]. An excessive calorie intake as compared to calorie expenditure in the body causes an increase in body weight which is characterized by an increase in white adipose tissue and can also lead to a decrease in the BDNF levels [27]. Having proven by the results of a study by Lee *et al*. [40], the baseline BDNF levels in individuals with obesity are lower than that of in the individuals without obesity. Furthermore, a study conducted by Si *et al*. [32] reported that was associated with the decrease in BDNF levels in adolescents aged 18–20 years. Obesity can reduce serum neurotrophic factor levels and cause blood-brain barrier (BBB) dysfunction [41]. This leads to peripheral pro-inflammatory cytokines to pass through the BBB, causing central inflammation that occurs in the brain and causes damage to the nervous system [42].

Conclusion

Based on the results of the study, there is a negative correlation between serum BDNF levels and BMI, WHR, and inflammation levels (IL-6 and TNF-α) in female with obesity. The authors suggest that future researchers can reveal the physiological mechanism of correlation between serum BDNF and BMI, WHR, and inflammation levels (IL-6 and TNF-α) in female with obesity more detail. Further studies are needed to confirm the present findings.

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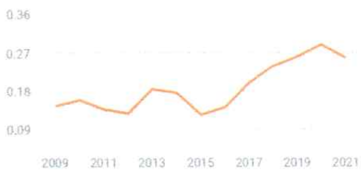

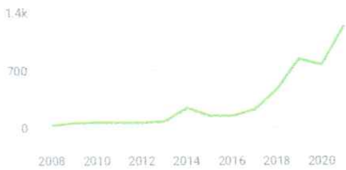

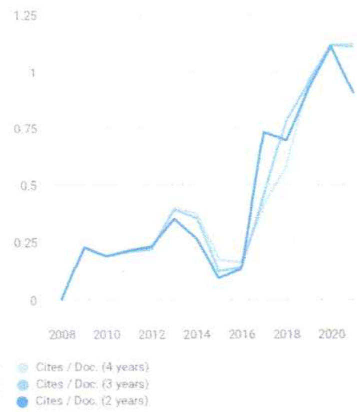

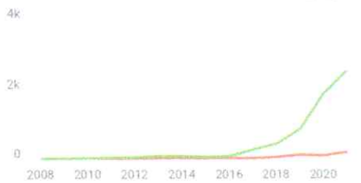

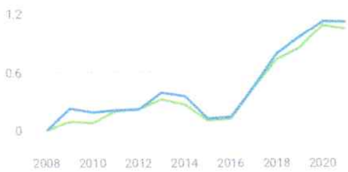

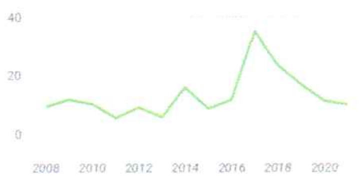

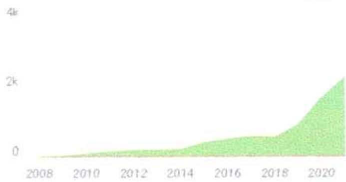

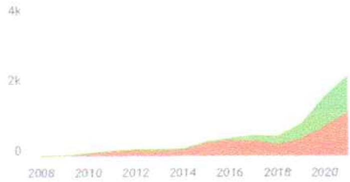

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